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ORIGINAL SCIENTIFIC REPORT

Evaluation of Parathyroid Glands with Indocyanine Green Fluorescence Angiography After Thyroidectomy

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Abstract

Background Indocyanine green fluorescence angiography (ICGA) is a new adjunct that has been used in surgical procedures to assess blood flow. This study evaluated the utility of ICGA compared to visual inspection to predict parathyroid function, guide autotransplantation and potentially decrease permanent hypoparathyroidism.

Methods This was a retrospective study of patients who underwent total or near-total thyroidectomy (T-NT) between January 2015 and March 2018. Patients with preoperative hyperparathyroidism and those undergoing reoperation were excluded. Patients who had ICGA were compared to T-NT patients without ICGA. Data were analyzed to assess the frequency of autotransplantation and incidence of hypoparathyroidism between groups.

Results In total, 210 patients underwent T-NT: 86 with ICGA and 124 without. Autotransplantation was more common in the ICGA group at 36% compared to 12% in the control ($p = 0.0001$). There was no correlation with at least one normal parathyroid gland on ICGA and postoperative PTH levels ($p = 0.75$). There was a difference in having normal postoperative PTH when there were at least two normal parathyroid glands ($n = 50$) compared to patients with less than two normal ICGA glands ($n = 36$, $p = 0.044$). Visual assessment and ICGA assessment of vascularity were in agreement, 245/281 (87%). There were 19 glands (6.8%) that would have undergone auto-transplant based on visual inspection that had adequate blood supply on ICGA. Transient hypoparathyroidism was present in 45 out of 124 controls (36%) and 32 out of 86 (37%) in the ICG group.

Conclusions ICGA is a novel technique that may improve the assessment of parathyroid gland blood supply compared to visual inspection. ICGA can guide more appropriate autotransplantation without compromising postoperative parathyroid function. At least two vascularized glands on ICGA may predict postoperative parathyroid gland function.

Introduction

Hypoparathyroidism is the most common complication after a total or near-total thyroidectomy (T-NT), [1]. It is usually due to unintentional removal or injury to the

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parathyroid glands or the blood supply [2]. The incidence of hypoparathyroidism has been associated with surgeon skill, experience, knowledge of parathyroid anatomy and the extent of resection [1]. Transient hypoparathyroidism is common, with a reported incidence of 6.9–46% [3]. The majority of patients with postoperative hypoparathyroidism will recover function in weeks to months with minimal sequelae. However, small subsets of patients develop permanent hypoparathyroidism, defined as persistent hypocalcemia 6 months postoperatively. Permanent hypoparathyroidism occurs in 0.9–6.6% and can lead to

lifelong dependency of calcium supplementation with an increased risk of osteoporosis and other adverse outcomes [3]. Intraoperative assessment of parathyroid gland viability has been limited to visual inspection, quantification of intraoperative PTH levels or sharp parathyroidotomy to assess for bleeding [4]. Detection of postoperative hypoparathyroidism has been achieved with PTH and calcium assays. Recently, indocyanine green angiography (ICGA) has been introduced as a potential modality to assess parathyroid viability intraoperatively [5–10]. Indocyanine green dye (ICG) was originally developed by Kodak Research laboratories in 1955 and approved for clinical research in 1956 [11]. ICG is a tricarbocyanine dye that is highly protein bound, remains in the intravascular compartment and undergoes first pass metabolism in the liver with excretion into bile [11, 12]. In addition, this inexpensive dye has a short half-life and is nontoxic, nonionizing and simple to use [11]. There have been several allergic and anaphylactic reactions reported in the literature, and these may be attributed to sodium iodine in the injection solution [11, 12]. ICGA was initially adopted into medical use by ophthalmology in the 1970s for imaging retinal vessels. Eventually, its utility has expanded across multiple surgical disciplines [11]. The use of ICGA in endocrine surgery is new, and data examining the correlation of intraoperative ICGA findings and postoperative parathyroid function are limited. We aimed to assess the utility of ICGA compared to visual inspection to assess parathyroid function, and therefore guide autotransplantation with a potential decrease permanent hypoparathyroidism.

Materials and methods

This was a single-center retrospective study of patients who underwent T-NT by a single surgeon (ML) between January 2015 and March 2018. Patients with preoperative hyperparathyroidism and those undergoing reoperation were excluded. The use of ICGA was introduced to the practice in March 2016 and used consecutively on patients undergoing a total thyroidectomy. Patients prior to this change in practice and those who did not have ICGA (due to unavailability of ICGA equipment) were selected for the non-ICGA group. Patients with intraoperative ICGA were compared to T-NT patients without ICGA.

All patients had a PTH level on postoperative day one to assess parathyroid function. Calcium levels were not checked on a routine basis and only obtained in patients exhibiting signs of hypocalcemia. All T-NT patients were initiated on calcium carbonate 500 mg elemental or calcium citrate 500 mg elemental per os (p.o.) three times per day in the immediate postoperative period. Calcium citrate

was used for patients with malabsorption or on proton pump inhibitors. The decision to discharge with calcium and possible calcitriol supplementation was determined by their postoperative day one PTH levels. Patients with PTH less than 10 pg/mL were started on elemental calcium 500 mg three times per day and calcitriol 0.50 mcg p.o. daily with follow-up PTH and calcium in approximately 2 weeks. These patients were all contacted by the endocrine surgery nurse when 2-week laboratory results were obtained to discuss symptoms and give calcium and calcitriol recommendations per the attending surgeon. Those who did not have their ordered lab tests collected were contacted and reminded to obtain their lab work. Patients with PTH levels 10–20 pg/mL were discharged on 500 mg elemental calcium p.o. three times per day with 2-week taper and no labs unless symptoms of hypocalcemia were developed. In patients with a PTH > 20 pg/mL, no calcium supplementation was continued on discharge.

Surgical technique

Patients in both groups underwent T-NT with or without cervical lymph node dissection. In the ICGA group, the parathyroid glands were identified after completion of T-NT and any lymph node dissection. There was no special attempt made to identify all four parathyroid glands. The viability of each gland was then assessed first using a visual evaluation followed by ICGA. For the visual assessment, each gland was determined to be viable or nonviable based on visual inspection and assigned a score of 2 (viable) vs 0 (nonviable), respectively. This was mainly based on the color of the gland. If the gland was slightly dusky but deemed viable, it was considered viable. Nonviable appearing glands were also those that would normally be deemed appropriate for autotransplantation. There was no parathyroidotomy done to check for the presence or absence of perfusion. Following visual inspection, the patients received 3 ml of ICG administered by the anesthesiologist through a peripheral access line, followed by 10 cc of saline wash. Approximately 1 min after administration, the parathyroid vascularity was evaluated using a laparoscopic PINPOINT camera (NOVADAQ, Ontario, Canada) and graded as none, intermediate or normal as described by Fortuny et al. [7] (Table 1). The administration of ICG was repeated using the same technique for the contralateral side. Additional dose was given as needed, up to 10 ml total of ICG. Glands with no ICGA uptake (score of 0) were autotransplanted, and a maximum of two glands were autotransplanted per patient. The autotransplant was performed by mincing up the parathyroid gland and implanting it subfascially within the sternocleidomastoid muscle.

Table 1 Intraoperative parathyroid gland scoring

ICG Score	Description
ICG 0	Black (devascularized)
ICG 1	Gray/partial (partially vascular)
ICG 2	White (vascular)
Visual score	Description
V0	No vascularity
V2	Excellent vascularity

T-NT and vascularity grading of parathyroid glands were performed by one surgeon (ML). Data were analyzed to assess the frequency of autotransplantation and incidence of hypoparathyroidism between groups. Statistical analysis was performed using Fischer's exact test and t test to determine significance.

Results

Between January 2015 and March 2018, there were 210 patients that underwent totally thyroidectomy: 86 patients with ICGA and 124 without. There were no major differences between both groups in terms of demographics, preoperative, postoperative PTH and surgical indication (Table 2). The majority of patients in both groups underwent T-NT for malignancy, with papillary thyroid cancer being the most common. Central compartment lymph node dissection (CLND), defined as level VI lymphadenectomy, was performed in 46% of patients in the non-ICGA group

Table 2 Demographics, preoperative and postoperative data

Demographics	Control	ICGA	P value
	($n = 124$)	($n = 86$)	
Age	49	47	$p = 0.43$
Sex ratio (M:F)	32:92	17:69	
Indications for surgery			
Malignant			
PTC	55%	48%	
MTC	2%	0%	
Follicular	6%	5%	
Hurthle	2%	3%	
Benign			
Multinodular Goiter	22%	27%	
Graves	13%	16%	
Mean POD 1 PTH	21.5 (pg/ml)	19.3 (pg/ml)	$p = 0.31$
Autotransplant	12%	36%	$p = 0.0001$
CLND[a]	45%	31%	$p = 0.065$

[a]Central lymph node dissection, level VI lymphadenectomy

compared to 31% in the ICGA group. There was no significant difference between CLND and postoperative PTH levels between the two groups ($p = 0.065$ and 0.31). Autotransplantation was more common in the ICGA group at 36% compared to 12% in the control ($p = 0.0001$). There were 19 glands (6.8%) that would have undergone autotransplantation based on visual inspection that had adequate blood supply on ICGA (Fig. 1). Visual assessment and ICGA assessment of vascularity were in agreement 245/281 (87%). Seventeen parathyroid glands (6.0%) had a normal visual score with no vascularity on ICGA, which resulted in autotransplantation these glands (Figure 1).

A postoperative day one PTH was found to be below the reference range (normal 15–65 pg/ml) in 36% of controls and 37% of ICGA patients. An undetectable PTH (PTH < 6 pg/ml) was present in 14% of control patients and 15% of ICGA patients. The mean postoperative day one PTH in the ICGA group was 19 pg/ml vs. 21 pg/ml in the control group. There were a total of 281 out 344 parathyroid glands identified (82%): All four glands were identified in 40 patients, three glands in 29 and two parathyroid glands in 17 patients.

Sixty-two out of 86 patients with intraoperative ICGA had at least one parathyroid gland with normal ICGA uptake. There was no correlation between having at least one or more normal parathyroid glands and postoperative PTH levels ($p = 0.75$). The accuracy of at least one normal gland on ICGA in predicting normal postoperative PTH was 57%, with a sensitivity of 58% (95% CI 44.85–70.49%) and specificity of 50% (95% 21.09–78.91%).

Fifty out of 86 patients with intraoperative ICGA had at least two parathyroid glands with normal ICGA uptake, which correlated with postoperative PTH levels ≥ 15 in 36 patients and PTH < 15 in 14. There was a difference having normal postoperative PTH when compared to patients with less than two normal ICGA glands ($n = 36$, $p = 0.044$) (note: < 2 normal includes patients with ICGA intermediate glands). The accuracy of two or more normal glands on ICGA in predicting normal postoperative PTH was 63%, with a sensitivity of 72% (95% CI 57.51–83.77%) and specificity of 50% (95% CI 32.92–67.08%)

The visual assessment did not show a correlation with having at least two normal glands on visual inspection ($n = 78$) and normal postoperative PTH function, compared to at less than two normal glands on visual inspection ($p = 0.25$).

Biochemical hypoparathyroidism, defined in this study as postoperative PTH < 15 (reference range 15–65 pg/ml), was present in 45 out of 124 controls (36%) and 32 out of 86 (37%) in the ICG group. There were 13 (15%) patients with PTH in the undetectable range (< 6) in the ICGA
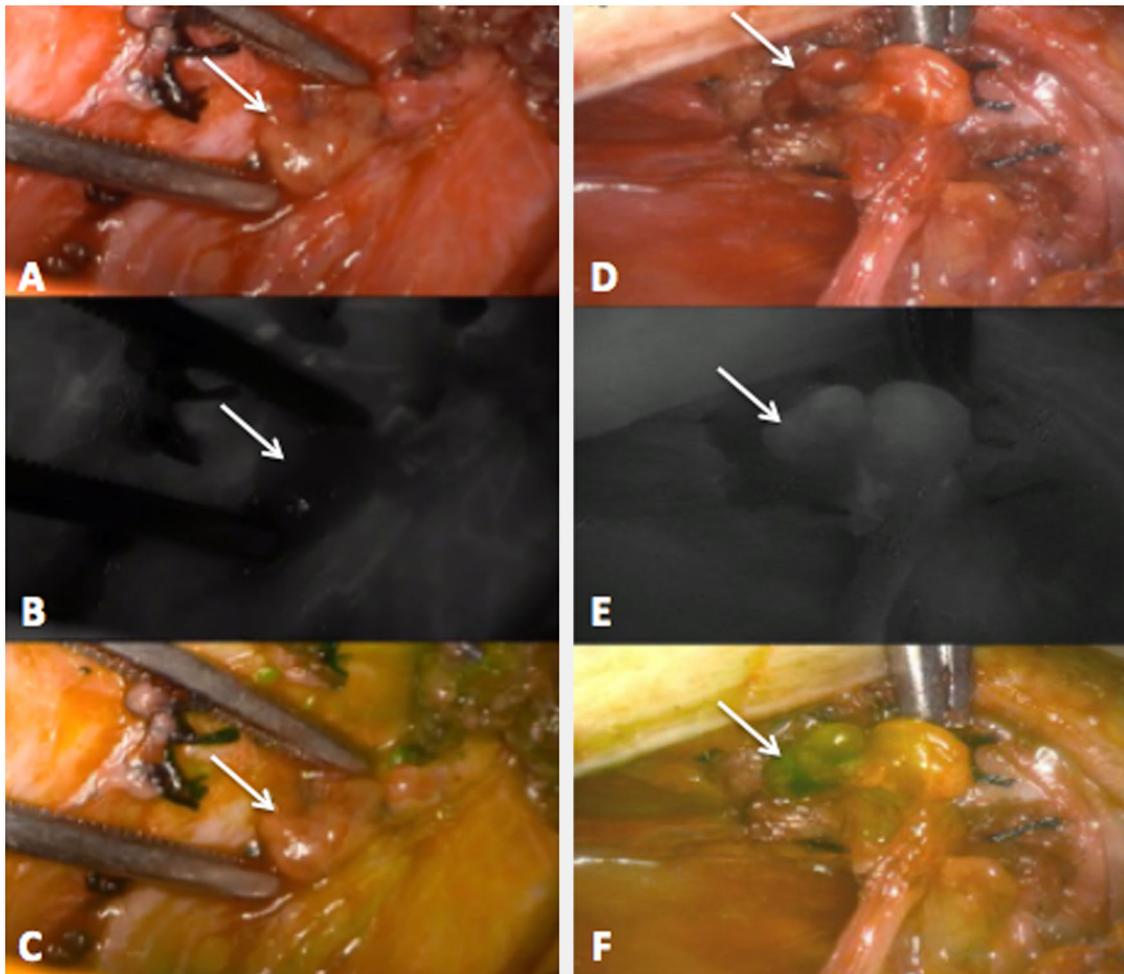
Fig. 1 Image of intraoperative parathyroid gland (white arrow) assessment. **a** Visual inspection shows parathyroid gland with a visual score of 2. **d** Visual inspection with a score of 0. **b, c** ICGA score of 0 and **e, f** ICGA score of 2. Images **a**, **b**, **c** are of the same parathyroid gland with a visual inspection of 2 (**a**) and discordant ICGA score of 0 (**b, c**). Images **d**, **e**, **f** are of the same parathyroid gland with a visual inspection of 0 (**d**) and discordant ICGA score of 2 (**e, f**)

group and 12 (10%) in the control group. In the ICGA group, 10 patients with undetectable postoperative PTH had transient hypoparathyroidism and were off supplementation within 6 months. One patient has persistent hypoparathyroidism and remains on calcium and calcitriol with a PTH of 6 pg/ml; two patients were lost to follow-up. The 2-week PTH levels ranged from 6 to 29 pg/ml (mean 12.6 pg/ml) in patients with undetectable PTH. Of all 32 patients with PTH levels below the reference range, 29 are off supplementation, one patient remains on supplementation and two lost to follow-up. Of the 45 patients in the control group, with PTH levels below the reference range, one patient had persistent hypoparathyroidism.

Discussion

Postoperative hypoparathyroidism is the most common complication after T-NT [2]. Parathyroid glands have a very tenuous blood supply and are prone to infarction with intraoperative manipulation [13]. Therefore, careful dissection and preservation of parathyroid glands found during T-NT have been the standard to preserve parathyroid gland function. In addition, identification of risk factors, such as need for lymphadenectomy, hyperthyroidism and multinodular goiter, can aid in predicting patients with increased risk of postoperative hypoparathyroidism [1]. To reduce the risk of postoperative hypoparathyroidism, some have reported that an elective parathyroid autotransplantation guided by intraoperative visual inspection and IOPTH levels may be beneficial [4, 14]. Although a low post-T-NT IOPTH has been reported as the earliest predictor of postoperative hypocalcemia [15], the accuracy of

PTH is higher when it is obtained greater than 6 h post-operatively [16]. Therefore, the use of IOPTH in identifying patients at risk of postoperative hypoparathyroidism is limited. Furthermore, it takes approximately 20 min to obtain an IOPTH result and it cannot be used to provide real-time assessment of individual parathyroid function. On the other hand, ICGA allows real-time assessment of parathyroid viability within minutes of the ICG injection [5, 7, 9], which confers a potential cost advantage of using intraoperative ICGA.

The definition of postoperative hypoparathyroidism is controversial. Calcium levels had previously been routinely obtained. However, most patients treated prophylactically had a normal serum calcium level the following morning, whether or not the PTH is normal or undetectable. Serum calcium levels may also take several days to decline. Patients may have clinical hypoparathyroidism with symptoms of hypocalcemia, biochemical hypocalcemia and normal or low PTH levels. The PTH level has been shown to be the earliest predictor for the development of symptomatic hypocalcemia. A PTH level below the normal range (biochemical hypoparathyroidism) is predictive of hypocalcemia. It allows the provider to provide adequate supplementation to help prevent symptomatic hypocalcemia. The incidence of hypoparathyroidism would be falsely low if a low serum calcium level was required to define post-thyroidectomy hypoparathyroidism. To accurately meet this definition would require that calcium be withheld from the patient. This would be an increased risk for the patient and prolong hospitalizations in order to manage symptomatic hypocalcemia. For these reasons, a biochemical assessment of hypoparathyroidism with a PTH level below the reference range was the most accurate and safe definition of postoperative hypoparathyroidism.

In this study, we analyzed the utility of ICGA in predicting postoperative parathyroid function and to guide autotransplantation in patients undergoing T-NT. Fortuny et al. reported that the identification of at least one gland with an ICGA viability of 2 was 100% predictive of normal parathyroid function postoperatively [7]. We did not find this correlation, and our data suggest that patients with at least one normal gland had an accuracy of 57% and a sensitivity of 58%. However, when patients had at least two glands with ICGA scores of 2, the accuracy and sensitivity were increased by 63% and 72%, respectively. At least two or more glands detected on ICGA correlated with normal postoperative PTH levels. However, it was not 100% predictive and therefore cannot be utilized as a sole method for predicting postoperative hypoparathyroidism. One of the limitations of this study and difference in results may be attributed to the short learning curve of interpreting the ICGA results, which may be subjective when assessing shades of gray or green. We found that the grayscale was more objective than the superimposed green fluorescence. The degree of vascularity was easier to differentiate in shades of black and white depending on the amount of ICG flowing through. The parathyroid glands appeared black with no perfusion, gray with some perfusion or white with full perfusion.

Conservation of all four parathyroid glands during T-NT has been shown to decrease the incidence of transient hypoparathyroidism, and preserving at least one parathyroid gland with an intact blood supply can be enough to prevent permanent hypoparathyroidism [17]. Accurate assessment of parathyroid vascularity has the potential to guide appropriate autotransplantation, while preserving viable parathyroid glands in situ. The use of ICGA has been shown to better assess perfusion than visual inspection for bowel resection and reconstructive procedures, resulting in improved clinical outcomes [18–20]. This may also be true for assessing parathyroid glands. In our study, approximately 12.4% of patients had an inaccurate visual assessment of their parathyroid glands. Of these, 17 parathyroid glands that visually appeared "normal" had no vascularity on ICGA and 18 glands which visually appeared "nonviable" had adequate blood supply on ICGA. Based on these data, ICGA seems to be more objective than visual inspection at detecting parathyroid gland viability and provides a unique advantage of ICGA over other methods of parathyroid assessment. However, the discordance between visual assessment and ICGA may represent evidence of transient ischemia and can pose a dilemma when deciding whether or not to proceed with autotransplantation which is a limitation of this test which needs to be further explored. It should also be noted that the differences may be more significant for low-volume surgeons and ICGA may be helpful for less experienced surgeons to assess parathyroid viability.

A parathyroidotomy has also been used by surgeons to assess the vascularity of parathyroid glands. This procedure involves an incision on the parathyroid gland to confirm bleeding. The ICGA assessment is advantageous over parathyroidotomy because it does not increase the risk of bleeding. Bleeding parathyroid glands will often require cauterization, which can damage parathyroid tissue.

The impact ICGA has on reducing rates of transient and permanent hypoparathyroidism is difficult to discern, especially given the low incidence of permanent hypoparathyroidism. Higher volume of patients would be required to detect those differences. The use of ICGA has continued in our practice, as it is felt to more accurately predict the viability of parathyroid glands to help guide parathyroid autotransplantation and identify patients at risk of hypoparathyroidism.

Conclusion

ICGA is safe, inexpensive adjunct that provides real-time intraoperative assessment of parathyroid gland blood supply, with the potential for guiding more appropriate autotransplantation. Our study suggests that at least two vascularized glands on ICGA correlate with normal postoperative parathyroid hormone levels and may predict parathyroid gland function. Further research is needed to determine whether ICGA reduces the risk of postoperative hypoparathyroidism.

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